IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Brenda F. Baker et al.

Confirmation No.: **7033**

Application No.: **10/701,265**

Group Art Unit: **1635**

Filing Date: **November 4, 2003**

Examiner: **Jennifer S. Pitrak**

For: **Chimeric Oligomeric Compounds and Their Use In Gene Modulation**

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

For the reasons discussed in the attached sheets, appellants respectfully request a pre-appeal brief conference for review and reconsideration of the official action issued December 9, 2010 in which claims 120, 121, 124, 127, 136, 137, and 138 of the above-identified patent application were finally rejected.

This request is being filed with a notice of appeal, no amendments are being filed with this request, and no more than five sheets of remarks are attached.

REMARKS

Claims 120, 121, 124, 127, 136, 137, and 138 were finally rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Lee, et al., *Cell*, 1993, 75, 843-854 ("Lee"), Manche, et al., *Mol. Cell Biol.*, 1992, 12, 5238-5248 ("Manche"), published PCT application number WO 94/01550 ("Agrawal"), and U.S. Patent Number 5,801,154 ("Baracchini") in the official action issued December 9, 2009. This rejection is based upon a legal error because the Examiner failed to identify reasons that would have led one skilled in the art to combine the cited references, and to then produce the claimed compounds in light of the references' combined teachings. Instead, without actually articulating such reasons, the Examiner asserted that "RNAs that form duplex structures were known to those in the art and used for a variety of purposes."[1] The Examiner thus implied that one of skill in the art would have combined the cited references and produced the claimed compounds so that the compounds could be used for the purposes described in the references, which are to study enzyme structure and regulation of gene expression. As discussed in the previously filed declaration of Dr. David Corey,[2] however, and as is evident from the cited references themselves, the claimed compounds would have been expected to have been unsuitable for such uses.[3] But the Examiner dismissed Dr. Corey's remarks on this point because the claims do not require that the oligomeric compounds exhibit any particular activity.[4] Since the rejection appears to rely on the uses described in the cited references as the reason why one would have combined the references to arrive at the claimed compounds, the expected unsuitability of the claimed compounds for such uses is actually highly relevant.

Significantly, nothing in the cited references, when considered individually or in combination in view of the state of the art at the time of the invention, would have prompted one skilled in the art to produce the claimed oligomeric compounds at that time. As discussed above, however, the examiner cited Lee "to demonstrate that at the time of filing, RNAs that form duplex structures were known to those in the art and used for a variety of purposes."[5] But as

[1] Office action dated December 9, 2009, page 4.
[2] Declaration of David Corey, filed August 18, 2009.
[3] Declaration of David Corey, paragraphs 15, 19, 24, 28, and 29.
[4] Office action dated December 9, 2009, pages 5 and 6.
[5] Office Action dated December 9, 2009 at page 4.

carefully explained by Dr. Corey, one of skill would have expected the claimed compounds to have been unsuitable for furthering any of the purposes discussed in Lee.[6] Accordingly, to the extent that the Examiner relied on Lee to provide a reason for arriving at the claimed compounds, that reliance is misplaced.

Lee describes two transcripts encoded by the *C. elegans lin-4* gene: the 61 nucleotide-long *lin-4*L and the 22 nucleotide-long *lin-4*S. According to Lee, the transcripts are each partially (but not fully) complementary to *lin-14,* the expression of which Lee proposes is regulated by *lin-4*. Lee speculates that it is the shorter of the two transcripts, *lin-4*S, that is responsible for regulating *lin-14* expression. As explained by Dr. Corey, if one had wanted to further study the possible role of *lin-4S* at the time of the invention, one would not have made compounds such as those claimed.[7] For example, one would have had no reason to produce a compound having a base sequence fully complementary to the target, as claimed. More significantly, one would not have paired *lin-4S* with a complementary strand to form a duplex, as also claimed. Rather, as taught by Lee, one would have expected that such a complementary strand would interfere with the proposed mechanism of action: hybridization of the *lin-4S* transcript with the *lin-14* message. Accordingly, Lee's discussion of *lin-4S* would have provided no reason to arrive at the claimed compounds and would have even discouraged the production of such compounds.

Lee describes the *lin-4L* transcript as having a stem-loop structure in which two complementary regions of the transcript form a duplex – a stem – connected by a non-complementary loop region.[8] Lee suggests that because of this structure, *lin-4L* is likely not the transcript responsible for regulating *lin-14*. Even if one were to have disregarded this teaching in Lee, and further investigated the potential role of *lin-4L*, one still would have had no reason to produce the claimed compounds. The claims recite duplexes comprising separate oligomeric compounds, and not single self-complementary compounds. Dr. Corey explains that such molecules would have been expected to have very different properties, and enzymes that interact

[6] Declaration of David Corey, paragraphs 11 to 15.
[7] Declaration of David Corey, paragraph 9.
[8] Figure 8.

with one would not have been expected to interact with the other.[9] Thus, even if one had wanted to further study *lin-4L*, despite Lee's suggestion that it is not the active transcript, one still would have had no reason to alter the structure of that molecule to arrive at a compound claimed. As Dr. Corey makes clear, nothing in Lee, either alone or in view of the other references, would have prompted one of skill in the art to make the claimed compounds.

Likewise, nothing in Manche, alone or in combination with the other cited references, would have prompted one of skill to arrive at the claimed oligomeric compounds. Manche describes RNA duplexes bound by interferon-induced protein kinase DAI. None of the RNAs in the duplexes described in Manche is 100 % complementary to a target mRNA as claimed, and because the RNA binding properties of DAI were sequence independent, there would have been no reason to make duplexes having 100% complementarity to a target mRNA.

More significantly, Manche actually discourages the production of RNA duplexes of the length claimed. Manche studied unmodified RNA duplexes of 15 to 104 nucleotides to determine the effect of length on DAI binding, and reports that duplexes shorter than 33 nucleosides failed to bind DAI.[10] Accordingly, one would have had no reason to prepare duplexes less than 33 nucleosides to study DAI activity. The Examiner asserted, however, that "whether such compounds were able to activate DAI is not at issue in the application; the claims are not directed to compounds having any particular activity."[11] Appellants again submit that if the reason for combining the cited references would have been to produce compounds useful for assessing the activity of DAI, then it is certainly relevant that one of ordinary skill would have expected compounds of the length claimed to be unsuitable for this use.

None of the duplexes described in Manche comprises modified nucleosides, as recited in the claims, and the Examiner offered no reasonable explanation as to why one would have been prompted to incorporate modified nucleosides into oligonucleotides of the length claimed. Puzzlingly, the Examiner offered only that one would have combined the teaching of Manche with teachings in the art of stabilizing modifications because "[w]hile it is correct that the compounds of Manche were enzymatically synthesized, the reason to make chemically modified

[9] Declaration of David Corey, paragraphs 11 to 13.
[10] Abstract and figure 1.
[11] Office Action dated December 9, 2009 at pages 4 to 5.

oligonucleotides comes from the knowledge in the art that stabilization of oligounucleotides is desirable."[12] The Examiner offered no reason why it would have been desirable to stabilize inactive compounds, however.

The Examiner further cited two references, Agrawal and Baracchini, that describe compounds useful for RNase-H dependent mRNA inhibition. Each of these references describes several specific compounds with activity in this mechanism, and each generally describes other compounds, including compounds having broad length ranges and numerous possible chemical modifications. As noted by Dr. Corey, the claimed compounds differ in important ways from those of Agrawal and Baracchini.[13] Because of those differences, one of ordinary skill would have expected the claimed compounds to fail as RNase-H dependent inhibitors. Once again, the Examiner labeled this assessment irrelevant to the rejection, reasoning that because the claims do not recite a particular use for the oligomeric compounds, it makes no difference that they would have been expected to fail in the uses described in Agrawal and Baracchini.[14] Thus, the Examiner again relied on a particular use described in the cited references for providing the reason for arriving at the claimed compounds, but disregarded evidence that one of ordinary skill in the art would have expected that the claimed compounds would have been unsuitable for that use.

Rather than explain why one would have been prompted to make the claimed compounds, the Examiner instead cited various references that separately show each claim feature, and then concluded that one skilled in the art would have combined the references, and the combined teachings of the references would have rendered the claimed compounds obvious. Neither the references themselves nor the facts of record support this conclusion. As made clear from the Declaration of Dr. Corey, one of ordinary skill would not have combined the chemical modifications discussed in Baraccinni and Agrawal with the duplexes discussed in Lee and Manche to further the purposes described in any of the references.[15] Specifically, one would not have incorporated the modifications or sequence complementarity of Baraccinni and Agrawal

[12] Office Action dated December 9, 2009 at page 5.
[13] Declaration of David Corey, paragraphs 20 to 28.
[14] Office Action dated December 9, 2009 at pages 5 to 6.
[15] Declaration of David Corey, paragraph 29.

into the duplexes of Manche, because there would have been no reason to stabilize duplexes to determine whether they activate DAI *in vitro* via a sequence-independent mechanism. Likewise, one would not have used duplexes such as those discussed by Manche in the RNase H-dependent work described in Baraccinni and Agrawal, because the second strand of the duplexes would have been expected to interfere with RNase H activity. And the claimed compounds would not have been expected to be useful for studying the natural transcripts described in Lee.

Dr. Corey concluded that "none of the cited references nor all of them in the aggregate would have prompted me, or a comparably skilled scientist in the field, to make a duplex having two separate, fully complementary oligonucleotides, where one of them is complementary to a target mRNA, each is from 15-25 nucleosides in length, each has at least one modified nucleoside and at least one has a plurality of ribonucleosides."[16] Since the Examiner failed to identify a reason why one of skill in the art would have combined the cited references to arrive at the claimed compounds, the present rejection is improper and should be withdrawn.

Respectfully submitted,

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[16] Declaration of David Corey, paragraph 29.